

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |   |   |
|---|---|---|
| (51) International Patent Classification <sup>5</sup> :<br>A01N 33/12, 43/40  | A1  | (11) International Publication Number: WO 94/22305<br>(43) International Publication Date: 13 October 1994 (13.10.94) |
| (21) International Application Number: PCT/EP94/00821<br>(22) International Filing Date: 15 March 1994 (15.03.94)<br>(30) Priority Data:<br>9306806.2 1 April 1993 (01.04.93) GB<br>(71) Applicant (for all designated States except AU BB CA GB IE LK MN MW NZ SD): UNILEVER N.V. [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).<br>(71) Applicant (for AU BB CA GB IE LK MN MW NZ SD only): UNILEVER PLC [GB/GB]; Unilever House, Blackfriars, London EC4 4BQ (GB).<br>(72) Inventors: BELLAMY, Kathryn; 20 High Street, Carlton Bedford MK43 7LA (GB). ALCOCK, Robert; 9 Milton Close, St. Ives, Cambs PE17 3QX (GB). LABAN, Kevin, LeslieHUDSON, Ronald, Archie; Bernard Zweerslaan 6, NL-2253 BN Voorschoten (NL).<br>(74) Common Representative: UNILEVER N.V.; Patent Division, P.O. Box 137, NL-3130 AC Vlaardingén (NL). | (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br>Published<br>With international search report. |   |
| (54) Title: DISINFECTANT COMPOSITIONS<br>(57) Abstract<br><p>There is provided an aqueous virucidal composition suitable as hospital disinfectant, comprising alkaline material and from 0.01 to 5 % by weight of an alkyl quaternary nitrogen salt, and having a pH in the range of 10-12. This composition was found to be effective for killing non-enveloped viruses such as polio viruses, and for disinfecting heat sensitive medical instruments, such as flexible endoscopes.</p>   |   |   |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |                          |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria                  | GB | United Kingdom                           | MR | Mauritania               |
| AU | Australia                | GE | Georgia                                  | MW | Malawi                   |
| BB | Barbados                 | GN | Guinea                                   | NE | Niger                    |
| BE | Belgium                  | GR | Greece                                   | NL | Netherlands              |
| BF | Burkina Faso             | HU | Hungary                                  | NO | Norway                   |
| BG | Bulgaria                 | IE | Ireland                                  | NZ | New Zealand              |
| BJ | Benin                    | IT | Italy                                    | PL | Poland                   |
| BR | Brazil                   | JP | Japan                                    | PT | Portugal                 |
| BY | Belarus                  | KE | Kenya                                    | RO | Romania                  |
| CA | Canada                   | KG | Kyrgyzstan                               | RU | Russian Federation       |
| CF | Central African Republic | KP | Democratic People's Republic<br>of Korea | SD | Sudan                    |
| CG | Congo                    | KR | Republic of Korea                        | SE | Sweden                   |
| CH | Switzerland              | KZ | Kazakhstan                               | SI | Slovenia                 |
| CI | Côte d'Ivoire            | LI | Liechtenstein                            | SK | Slovakia                 |
| CM | Cameroon                 | LK | Sri Lanka                                | SN | Senegal                  |
| CN | China                    | LU | Luxembourg                               | TD | Chad                     |
| CS | Czechoslovakia           | LV | Latvia                                   | TG | Togo                     |
| CZ | Czech Republic           | MC | Monaco                                   | TJ | Tajikistan               |
| DE | Germany                  | MD | Republic of Moldova                      | TT | Trinidad and Tobago      |
| DK | Denmark                  | MG | Madagascar                               | UA | Ukraine                  |
| ES | Spain                    | ML | Mali                                     | US | United States of America |
| FI | Finland                  | MN | Mongolia                                 | UZ | Uzbekistan               |
| FR | France                   |    |  | VN | Viet Nam                 |
| GA | Gabon                    |    |  |    |                          |

## DISINFECTANT COMPOSITIONS

### FIELD OF THE INVENTION

The invention relates to disinfectant compositions. More  
5 specifically, it relates to aqueous disinfectant compositions containing an alkyl quaternary nitrogen salt in the presence of an alkaline component.

The invention is particularly suitable to be used for  
disinfecting objects and surfaces at locations where con-  
10 tamination is of major concern, such as in hospitals, in the food and beverage industry and in the veterinary field.

### PRIOR ART AND BACKGROUND OF THE INVENTION

It is known that compositions comprising a quaternary am-  
15 monium halide and a sodium carbonate can be effectively used as anti-bacterial disinfectants.

FR-A-2 229 426 (Reusse) discloses an anti-bacterial auto-  
biodegradable disinfectant composition comprising 0.1-0.2%  
20 by weight of a quaternary ammonium chloride and 35 -40% by weight of sodium carbonate.

DE-A- 2 512 835 (Milbradt) discloses a granular germicidal  
disinfecting hospital laundering composition comprising one  
or more quaternary ammonium compounds and sodium carbonate.

25

It is an object of the present invention to provide an  
anti-viral composition having low toxicity and low cor-  
rosivity.

It is a further object of the invention to provide an anti-  
30 viral composition which shows effective killing ability with respect to non-enveloped hydrophilic viruses, particularly polio-viruses. It is another object of the invention to provide an anti-viral composition which can be effectively applied as an hospital disinfectant.

35 It was surprisingly found that these and other objects could be achieved with a composition according to the present invention.

#### DEFINITION OF THE INVENTION

The present invention relates to the use of an aqueous composition containing an alkaline material selected from alkali metal carbonates and alkali metal hydroxides, and  
5 from 0.01 to 5% by weight of an alkyl quaternary nitrogen salt, and having a pH in the range of from 10-12, as an anti-viral agent. Furthermore, the invention provides an aqueous virucidal composition suitable as hospital disinfectants, comprising alkaline material selected from alkali  
10 metal carbonates and alkali metal hydroxides, and from 0.01 to 5% by weight of an alkyl quaternary nitrogen salt, and having a pH in the range of 10-12.

#### DETAILED DESCRIPTION OF THE INVENTION

15 It is known that aqueous compositions containing alkyl quaternary nitrogen salts, particularly quaternary ammonium compounds exhibit some cleaning and bactericidal activity. However, a disadvantage of these compositions is that they are not able to inactivate uncoated viruses such as polio-  
20 viruses. It has now been found that addition of an alkaline material selected from alkali metal carbonates and hydroxides, to these compositions such that their pH is raised up to values in the range of 10-12, not only increases the disinfecting characteristics but also has a  
25 pronounced effect on the virucidal ability thereof. In this context, an aqueous composition is defined to be a composition containing at least 90% water.

#### The use of the composition of the invention

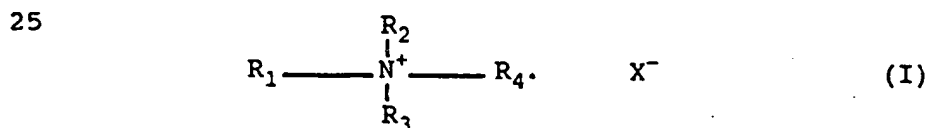
30 The aqueous composition of the invention was found to be very effective when used for killing non-enveloped viruses, in particular polio viruses. The effectiveness of the composition was reduced when it was applied in the presence of serum, but this effect could be overcome by the addition of  
35 an alkanol solvent selected from the group of ethanol, isopropanol, and n-propanol.

The product according to the invention is intended for use in high risk areas where contamination is of major concern, such as in human health care, veterinary health care and the food industry. The product is particularly suitable for use as disinfectant of medical instruments, especially of flexible endoscopes and similar heat-sensitive delicate instruments, that may be contaminated with viruses. The reason for this applicability of the product of the invention, is that both its toxicity and its aggressivity to delicate instruments are low.

The quaternary nitrogen salt

The alkyl quaternary nitrogen salt present in the aqueous virucidal composition of the invention may be selected from a broad range of compounds which contain at least one alkyl quaternary nitrogen group, and of which a common characteristic is their surface activity caused by the (at least one) alkyl group present therein. Particularly suitable compounds are ammonium salts, pyridinium salts, and quinolinium salts.

Preferably, the quaternary nitrogen salt is selected from compounds of the formulas (I) or (II):



wherein:

- 35  $\text{R}_1$  is a saturated or unsaturated, branched or linear alkyl group having 10-18 carbon atoms;  
 $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  are methyl, benzyl, substituted benzyl, or

saturated or unsaturated, linear or branched alkyl groups having 10-18 carbon atoms;

X<sup>-</sup> is a halide ion.

- 5 The level of the alkyl quaternary nitrogen salt present in the aqueous virucidal composition is generally in the range of from 0.01 to 5% by weight, preferably from 0.02 to 1% by weight.

- Favourable results, particularly with regard to the  
10 virucidal activity on uncoated viruses, were found when at least one quaternary ammonium halide is contained in the composition of the invention, said halide being preferably a dialkyl quaternary ammonium halide. Furthermore, the halide in those quaternary ammonium compounds is desirably  
15 a chloride or a bromide.

#### The alkaline material

- Generally, the level of the alkaline material in the composition of the invention is to be such that the pH is in  
20 the range of from 10 to 12. Depending on the type of alkaline material, a suitable level of such material is in the range of from 0.2 to 10% by weight.

- Generally alkali metal carbonates and hydroxides are applied as alkaline material in the composition of the invention.  
25 tion. Preferred types of alkaline material for use in the composition of the invention, are sodium carbonate and sodium hydroxide, for reasons of availability.

#### Anti-viral activity

- 30 It is an essential feature of the disinfectant compositions of the invention that the incorporation of an alkaline salt into a disinfectant containing a surface active quaternary nitrogen compound should bring about an improvement of the anti-viral activity. The anti-viral activity of various  
35 disinfectant compositions on the polio-virus is assessed using the DVV test, as described in Bundesgesundheits Blatt  
25 No 12, 1982, p.297.

The alkanol solvent

The alkanol solvent is not only suitable for restoring the effectiveness of the virucidal composition when applied in the presence of a serum. It can also be effectively applied for avoiding inactivation of the virucidal composition of the invention by organic soil. Suitable types of alkanol compounds are in this respect ethanol, iso-propanol and n-propanol. The alkanol is preferably present in an amount of from 10 to 30% by weight of the virucidal composition.

10

The invention will be further illustrated by the following non-limiting examples wherein parts and percentages are by weight, unless otherwise indicated.

15 In these examples the following abbreviations are used:

BARDAC 22 : dialkyl dimethyl quaternary ammonium  
chloride (50% active), ex Lonza

$\text{Na}_2\text{CO}_3$  : sodium carbonate

$\text{K}_2\text{CO}_3$  : potassium carbonate

20

Comparative Examples A,B

For the purpose of comparison, the virucidal activity of two different demineralised aqueous disinfectant solutions of BARDAC 22 against the polio-virus type 1 (Mahoney strain), was tested as follows.

25

Suspension tests were carried out according to the guidelines of the Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten (published in: Hygiene and Medicine 9, 177-179 (1984)). The polio-virus was obtained from Natec, Hamburg, and Vero cells (Green Monkey Kidney) were purchased from Flow Laboratories.

30

35 The polio-virus was grown in confluent layers of Vero until complete cytopathic effect was observed. Cultures were then frozen and thawed, after which they were centrifuged to

remove cell debris. The supernatant was stored in aliquots at -70 °C. The virus content of the suspension was determined by titration.

- 5 Monolayers of Vero cells were cultured in 96 well microtitre plates in a 5% carbon dioxide atmosphere. Ten-fold dilutions of virus suspension were made in maintenance medium. One hundred microlitres of each dilution were added to a single well, five replicates of each dilution were  
10 made. Cell controls were included on every plate. The plates were incubated at 37 °C in a CO<sub>2</sub> incubator, observed daily and discarded after seven days. The virus titre was calculated from the Kärber formula (Lenette E.H. and Schmidt N.J., Diagnostic Procedures for Viral, Rickettsial  
15 and Chlamydial Infections, 5th Edition, p.32-35 (1979)).

The suspension tests were carried out at room temperature (20 °C) but, after appropriate contact times of respectively 2 and 5 minutes, dilutions were made in ice-  
20 cold medium.

Two suspensions of viruses having known titres of 6.7 and 6.3 as calculated using the Kärber formula ( $\log_{10} \text{TCID}_{50}/0.1 \text{ ml}$ :  $\log_{10}$  of 50% tissue culture infectious dose, per 0.1 ml), were used for the tests.

25 One volume of virus suspension was mixed with one volume of distilled water and eight volumes of aqueous disinfectant solution. The mixture was kept at 20 °C for the duration of the contact time applied.

30 After appropriate contact times, samples were taken and an initial 1:100 dilution was made by adding 0.1 ml to 9.9 ml medium, subsequent dilutions being made by adding 0.1 ml to 0.9 ml. All dilutions were made in ice-cold medium, and the  
35 tubes containing the dilutions were kept on ice until they were inoculated into cell cultures. One hundred microlitres per well, 5 replicates for each dilution.

The micro-titre plates were incubated at 37 °C in an incubator with a 5% CO<sub>2</sub> atmosphere, and examined daily until they were discarded on day 7. The polio virus titre for each contact time was calculated as before using the Kärber formula. The following results from these suspension tests were found.

| Example No. | aq.disinfect. solution contacted | Virus titre recovered after contact time of |        |
|-------------|----------------------------------|---|--------|
|             |                                  | 2 min.                                      | 5 min. |
| A           | 0.2 %wt sol. of BARDAC 22        | 6.5   | 5.9    |
| B           | 0.05 %wt sol. of BARDAC 22       | 6.1   | 6.5    |

#### 15 Examples 1-4

Several anti-viral disinfectant compositions according to the present invention were formulated, said compositions being demineralised aqueous solutions containing BARDAC 22 and sodium or potassium carbonate.

20

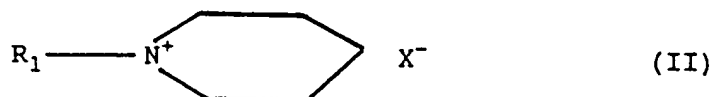
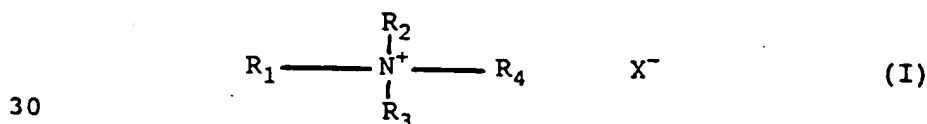
The virucidal activity of these aqueous solutions against the polio-virus type 1 (Mahoney strain), was tested following the procedure of the suspension test described in Examples A and B. The following results expressed in polio virus titres recovered after the appropriate contact times, and calculated using the Kärber formula, were obtained.

| Example No. | Aq. disinfect. solution including                      | Virus titre recovered after contact time of |        |
|-------------|--|---|--------|
|             |  | 2 min.                                      | 5 min. |
| 1           | 0.2% BARDAC 22 + 0.2% Na <sub>2</sub> CO <sub>3</sub>  | ≤ 2.5                                       | ≤ 2.5  |
| 2           | 0.05% BARDAC 22 + 0.2% Na <sub>2</sub> CO <sub>3</sub> | ≤ 2.5                                       | ≤ 2.5  |
| 3           | 0.2% BARDAC 22 + 0.2% K <sub>2</sub> CO <sub>3</sub>   | ≤ 2.5                                       | ≤ 2.5  |
| 35 4        | 0.05% BARDAC 22 + 0.2% K <sub>2</sub> CO <sub>3</sub>  | ≤ 2.5                                       | ≤ 2.5  |

When comparing Examples 1-4 with Comparative Examples A,B ,  
it can be concluded that, at both contact times applied,  
the aqueous disinfectant solutions of the invention and  
containing both BARDAC 22 and an alkali metal carbonate  
5 achieved a reduction of about 4 in the virus titre, as com-  
pared to the test results of the comparative disinfectant  
solutions containing only BARDAC 22.

CLAIMS

1. The use of an aqueous composition containing an  
5 alkaline material selected from alkali metal carbonates and  
alkali metal hydroxides, and from 0.01 to 5% by weight of  
an alkyl quaternary nitrogen salt, and having a pH in the  
range of from 10-12, as an anti-viral agent.
- 10 2. Use of the composition according to claim 1 for killing  
non-enveloped viruses, such as polio-viruses.
3. Use of the composition according to claim 1 for disin-  
fecting heat sensitive medical instruments, such as  
15 flexible endoscopes.
4. Aqueous virucidal composition suitable as hospital  
disinfectant, comprising alkaline material selected from  
alkali metal carbonates and alkali metal hydroxides, and  
20 from 0.01 to 5% by weight of an alkyl quaternary nitrogen  
salt, and having a pH in the range of 10-12.
5. Composition according to claim 4, wherein the quater-  
nary nitrogen salt comprises at least one compound of the  
25 formulas (I) or (II):



wherein:

R<sub>1</sub> is a saturated or unsaturated, branched or linear alkyl group having 10-18 carbon atoms;

R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are methyl, benzyl, substituted benzyl, or  
5 saturated or unsaturated, linear or branched alkyl groups having 10-18 carbon atoms;

X<sup>-</sup> is a halide ion.

6. Composition according to claim 5, wherein the quaternary  
10 nitrogen salt comprises at least one quaternary ammonium halide of the formula (I).

7. Composition according to claim 6, wherein the quaternary ammonium halide is a dialkyl quaternary ammonium halide.

15

8. Composition according to claim 6 or 7, wherein the quaternary ammonium halide contains a halide selected from the group consisting of chloride and bromide.

20 9. Composition according to any of claims 4-8, wherein the composition comprises from 0.02 to 1% by weight of the alkyl quaternary nitrogen salt.

10. Composition according to any of claims 4-9, wherein  
25 the composition comprises from 0.2 to 10% by weight of the alkaline material.

11. Composition according to any of claims 4-10, wherein the composition comprises from 10 to 30 % by weight of an  
30 alkanol selected from the group consisting of ethanol, isopropanol and n-propanol.

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/EP 94/00821

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A01N33/12 A01N43/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | US,A,3 941 696 (J.L. MELNICK ET AL.) 2<br>March 1976<br>see column 2, line 3 - line 10<br>see column 3, line 50 - line 53<br>---  | 1-5,9,10              |
| X,P        | CHEMICAL ABSTRACTS, vol. 119, no. 19,<br>8 November 1993, Columbus, Ohio, US;<br>abstract no. 195159q,<br>M. KAGEYAMA ET AL. 'inactivation activity<br>of various disinfectants against<br>infectious bursal disease virus'<br>see abstract<br>& CHIKUSAN NO KENKYU<br>vol. 47, no. 8, 1993<br>pages 929 - 931<br>---<br>-/-- | 1-10                  |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

\* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* "&" document member of the same patent family

Date of the actual completion of the international search

20 June 1984

Date of mailing of the international search report

01.07.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Decorte, D

# INTERNATIONAL SEARCH REPORT

Int. Application No.  
PCT/EP 94/00821

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|----------|--|-----------------------|
| X        | FR,A,2 139 074 (ROHM AND HAAS) 5 January 1973<br>see page 3, line 6 - line 8<br>see page 14; table 2<br>see claims 1,6<br>---- | 4-10                  |
| X        | DE,A,27 11 577 (CHEMED CORP.) 21 September 1978<br>see page 25; examples a-d<br>----   | 4-11                  |
| A        | DE,A,40 05 784 (SCHULKE & MAYR) 29 August 1991<br>see page 1, line 18 - line 30<br>----  | 1                     |
| A        | EP,A,0 190 797 (J.K. VOIT) 13 August 1986<br>see claim 1<br>-----  | 11                    |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/00821

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| US-A-3941696                              | 02-03-76            | US-A- 4043911              | 23-08-77            |
| FR-A-2139074                              | 05-01-73            | AU-A- 4277272              | 29-11-73            |
|   |                     | BE-A- 783920               | 27-11-72            |
|   |                     | CA-A- 965678               | 08-04-75            |
|   |                     | DE-A- 2225109              | 14-12-72            |
|   |                     | GB-A- 1348744              | 20-03-74            |
| DE-A-2711577                              | 21-09-78            | NONE                       |                     |
| DE-A-4005784                              | 29-08-91            | US-A- 5185145              | 09-02-93            |
| EP-A-0190797                              | 13-08-86            | NONE                       |                     |